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Original Research Article

A retrospective longitudinal study on the effect of ultra short course of steroid therapy on clinical and hematologic parameters of secondary hemophagocytic lymphohistiocytosis in children

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ABSTRACT

Background: The aim was to study the effect of ultra-short course of injectable steroid followed by oral steroid therapy for cumulative 14 days on clinical and hematologic parameters of secondary hemophagocytic lymphohistiocytosis in children.
Method: A retrospective longitudinal study was conducted by collecting data from case records. Cases diagnosed with secondary hemophagocytic lymphohistiocytosis had been included. The cases with malignancy were excluded. Remaining cases had been given injectable methyprednisolone (30 mg/kg/day) for three days followed by oral prednisolone (1 mg/kg/day) for 11 days. The time to cessation of fever and organomegaly were noted. The changes in mean hematologic parameters, ferritin and triglycerides were noted at the time of suspicion of HLH or MAS, after therapy and on follow up.
Results: About 96% of children were afebrile within five days of therapy. There was regression of hepatospleenomegaly in all 100% surviving children by day seven of therapy. Improvement in hemoglobin (mean value 8.1 mg/dl to 8.7 mg/dl) and platelet count (mean value 0.89 lakh to 1.47 lakh) was seen by day seven of therapy. Fall in serum ferritn (mean value 1419 ng/ml to 298 ng/ml) and serum triglycerides (mean value 307 mg/dl to 176 mg/dl) was seen at one-month follow-up. 96% survival was observed. None of the survivors had any recurrence at 6 months follow up.
Conclusion: Ultra short course of injectable methyprednisolone for 3 days followed by oral prednisolone for 11 days was successful in 95% survival in our study. This cost-effective regimen, with use of less toxic drugs leading to a shorter hospital stay maybe helpful in resource limited settings.

Keywords: Ferritn, Hemophagocytic lymphohistiocytosis, Injectable methyprednisolone, Macrophage activation syndrome, Oral prednisolone, Triglycerides

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) has been classified under Histiocytosis syndromes of childhood.[1] HLH is not a single disease but can be encountered in association with variety of underlying conditions (genetic and acquired) leading to same hyperinflammatory phenotype.[2] These disorders feature severe cytopenias due to uncontrolled hemophagocytosis. Other laboratory signs and clinical symptoms result from disordered

immune regulation and cytokine storm.[3] HLH is classically divided into two types primary or familial HLH and secondary HLH. Familial HLH is generally an autosomal recessive condition, whereas secondary HLH is usually associated with infectious diseases, autoinflammatory and autoimmune diseases (where it is more commonly known as macrophage activation syndrome), malignancy, immunosuppression, hematopoietic stem cell transplantation, organ transplantation, HIV infection, and metabolic diseases.[4]

Primary HLH is associated with mutations in genes expressing perforin and granzyme enzymes. Heterozygous patients for the perforin gene mutation may manifest the disease despite having normal perforin expression levels. Children with a strong family history of HLH also may be offered the test prophylactically. Prenatal and preimplantation diagnosis is possible by genetic analysis once the gene defect within a family is known. Mutations in other genes related to granule trafficking and exocytosis also can be determined by quantifying the expression of surface CD107a (LAMP-1) on paper peripheral blood mononuclear cells following stimulation with phytohemagglutinin or anti-CD3.[5]

Acquired HLH is often subcategorized into infection associated HLH, with particular emphasis on Epstein-Barr virus.[6] Macrophage Activation Syndrome (MAS) is a life-threatening complication of systematic onset juvenile idiopathic arthritis. The first mouse model of MAS not requiring infection but rather dependent on repeated stimulation through Toll-like receptors was reported by Ravelli et al. This provides a model of MAS that may more accurately reflect MAS pathology in the setting of autoinflammation or autoimmunity. This model confirms the importance of a balance between pro-and anti-inflammatory cytokines.

There has been remarkable progress in the use of anti-pro-inflammatory cytokine therapy, particularly against interleukin-1, in the treatment of secondary forms of MAS, such as in systemic onset Juvenile Idiopathic Arthritis (Sjia).[7] Clinical signs of HLH include prolonged high grade fever, multi-organ involvement including cytopenias, hepatosplenomegaly and liver dysfunction, skin rash, coagulopathy and variable neurologic symptoms.[8] HLH is diagnosed based on HLH diagnostic criteria-2004 (Table 1).[9]

Molecular diagnosis of Hemophagocytic Lymphohistiocytosis or the presence of at least 5 of 8 criteria: The presence of hemophagocytes in bone marrow is pathognomonic but may not be obvious at the time of initial diagnosis.

However, the prominent sinusoidal Kupffer cell hyperplasia and conspicuous hemophagocytosis with extramedullary hemopoiesis led to a strong suspicion of HLH in the absence of initial bone marrow hemophagocytes in a study by Chatura et al.[10]A possibility of HLH has to be taken into accounting any child who does not show the expected response to the therapy that has been initiated.[11]

Table 1: Diagnostic criteria of hemophagocytic lymphohistiocytosis.

Fever
Splenomegaly
Cytopenias (affecting at least 2 lineages in the peripheral blood), hemoglobin levels <90 g/L (in infants <4 weeks old, hemoglobin <100 g/L), Platelets <100×10 9/L and Neutrophils <1.0×109/L.
Hypertriglyceridemia and/or hypofibrinogenemia: Fasting triglycerides ≥3.0 mmol/L (ie, ≥265 mg/dL) Fibrinogen ≤1.5 g/L.
Documented hemophagocytosis in the bone marrow, spleen, or lymph nodes.
Low or absent natural killer cell activity.
Ferritin ≥500 mg/L.
Soluble CD25 (i.e. soluble interleukin-2 receptor) ≥2,400 U/mL.

Traditionally HLH-94 protocol was followed for the management of HLH. HLH-94 protocol included an initial intensive therapy with immunosuppressive and cytotoxic agents for eight weeks, with the aim to induce remission of the disease activity.[12] HLH-94 is very effective, allowing BMT in most patients. Survival of children with HLH has been greatly improved.[13] Other treatment modalities for treatment of HLH have been documented in literature. Liposomal doxorubicin treatment combined with etoposide and methylprednisolone showed an encouraging overall response and was well tolerated in adults according to the study by Wang et al.[14] Nawata et al, suggested the possibility of mycophenolate mofetil as a key drug for treating HLH associated with SLE.[15] According to study by Naoi et al additional therapy (with steroids/immunosuppressive drugs/ IVIg) was significantly more frequently provided in the pediatric group than in the adult group (p=0.012) in cases of scrub typus associated HLH.[16] Corticosteroids with disease specific therapy have been mentioned as the treatment for clinically stable cases of HLH [17]. However, the duration, dose and choice of steroids as monotherapy for management of HLH has not been established. Steroid therapy for one month was given in the case report by Giri et al.[18] With the above background, we present a study on Ultra-short course of injectable methylprednisolone followed by oral prednisolone therapy on children with secondary HLH.

METHODS

A retrospective longitudinal study was conducted over duration of two year. The study population comprised of children in age group 2 to 17 years diagnosed with secondary hemophagocytic lymphohistiocytosis based on

HLH 2004 guidelines[9]. Data was collected from case records of our Hospital (inpatient and outpatient). The cases with suspected malignancy, stigmata of primary HLH (albinism, premature graying of hair etc), family history of HLH or previous history of HLH had been excluded. Remaining cases had been given injectable methy prednisolone (30 mg/kg/day) for three days followed by oral prednisolone (1 mg/kg/day) for 11 days. The time to cessation of fever and organomegaly were noted. Specific statistical methods were not utilised as the patient population was less than 30 and the results were highly obvious on percentage values.

The changes in mean hematologic parameters on admission and 7 days after therapy were noted. The changes in Ferritin and triglycerides were noted at the time of suspicion of HLH and at one month follow up.

RESULTS

The study population was within the age group of 2 years to 17 years. The incidence in boys (64%) was higher when compared to girls (36%). Of the total 25 cases, 2 cases of malignancy were excluded. Of the remaining 23 cases, 21 cases were of infection and 2 cases were of juvenile idiopathic arthritis (Figure 1).

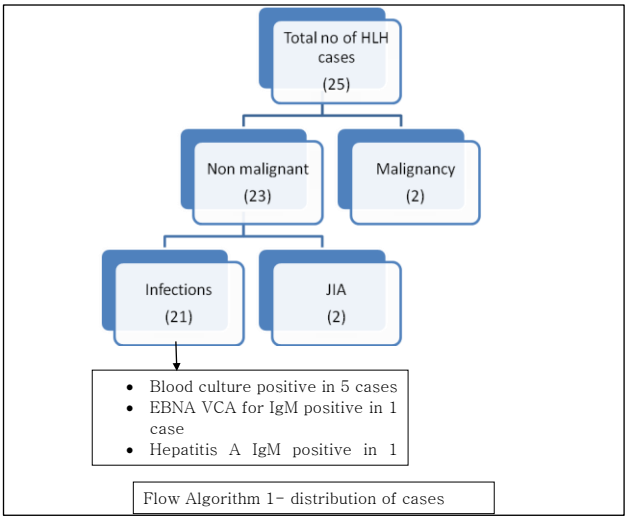

Figure 1: Molecular diagnosis of hemophagocytic lymphohistiocytosis or the presence of at least 5 of 8 criteria.

Blood culture was positive in 5 cases. EBNA VCA was positive for IgM in one case. Serology for hepatitis A was positive in one case. IgM for scrub typhus was positive in one case. The percentage of cases with various clinical and laboratory parameters has been elaborated in Table 2.

All 23 patients fulfilled the HLH 2004 criteria. Neutropenia was observed in 36% of the patients. 64% of the patients had coagulopathy. 28% were in incipient renal failure. All patients had elevated liver enzymes and hyperbilirubinemia was observed in 28%. 36% of the patients had respiratory symptoms, 8% were ventilated. 40% required ionotropes or vasopressers. Rash and lymphadenopathy were seen in almost 50% of the children. 96% of children were afebrile within five days of therapy. There was regression of hepatosplenomegaly in all 100% surviving children by day seven of therapy. Improvement in hemoglobin (mean value 8.1 mg/dl to 8.7 mg/dl) and platelet count (mean value 0.89 lakh to 1.47 lakh) was seen by day seven of therapy.

Fall in serum ferritn (mean value 1419 ng/ml to 298 ng/ml) and serum triglycerides (mean value 307 mg/dl to 176 mg/dl) were seen at one-month follow-up. Bone marrow study was done in 15 hemodynamically stable children, of which hemophagocytes were seen in 7 cases. 96% survival was observed.

Table 2: Clinical and Laboratory Parameters.

The percentage of study population with clinical and laboratory parameters of HLH	
Fever	100%
Spleenomegaly	100%
Hepatomegaly	95%
Anemia (hemoglobin <9 g/dl)	100%
Thrombocytopenia (platelet < 1 lakh/mm^3)	100%
Neutropenia (ANC <1000/mm^3)	36%
Hyperferritenimia (> 500 ng/dl)	100%
Hypertriglyceridemia (> 265 mg/dl)	100%
Elevated liver transaminases (>60 IU/L)	100%
Rash	52%
Lymphadenopathy	42%
Respiratory symptoms	36%
CNS symptoms	28%
Coagulopathy (prolonged PT and APTT)	64%
Hyperbilirubenimia (>2 mg/dl)	28%
High creatinine (>1.5 mg/dl)	28%
Hypotension	40%
Ventilation	8%

DISCUSSION

None of the children had any stigmata, prior history or family history of primary HLH and 100% of them had fulfilled five (fever, splenomegaly, cytopenia, hyperferritinemia, hypertriglyceridimia) out of the eight criteria of the HLH 2004 protocol.

Hence, were presumed to be secondary HLH. However, genetic testing could not be done in view of financial constraints. In the current study, there was improvement in both clinical and laboratory values after ultra short course of steroids. There was 95% survival. The results are better than the study by Ramachandran et al, where 22 out of 33 children diagnosed with HLH were started on IV steroids, followed by IVIG. 76% of the children survived.[19]

In another study by Demirkol et al, the use of plasma exchange and methyl prednisolone or intravenous immunoglobulin (n = 17, survival 100%) was associated with improved survival compared to plasma exchange and dexamethasone and/or cyclosporine and/or etoposide (n = 6, survival 50%). [20]

CONCLUSION

Present study showed a 96% survival with ultra-short course steroid therapy. A high index of suspicion and early initiation of this cost-effective therapy has use of lesser toxic drugs and leads to a shorter hospital stay and a better outcome. However, the promising results of our study have to be validated by further studies in a larger population.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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